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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/524,454	03/10/2000	Kristian Berg	697.013US1	5804

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/524,454	BERG ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2004 and 29 June 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments and remarks filed 3/26/04 have been entered.

2. Applicant indicates that Claim 1 has been withdrawn. However, as the claim no longer comprises any text, the claim is considered to have been canceled.

Claims 2-11 are pending and being acted being acted upon.

3. In view of Applicant's amendments and remarks, in particular, Applicant's indication that the photochemical internalization of the instant application is the photochemical internalization of the prior art, the previous rejections under the first paragraph of 35 U.S.C. 112 for lack of adequate written description have been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used for expressing a molecule on a cell, said method comprising photochemical internalization wherein the molecule is sufficient to generate an immune response, for the reasons of record as set forth in the papers mailed 4/24/01, 6/18/02, 2/10/03, and 1/24/03.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must

be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding novel methods involving biological processes, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)". The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the immunological arts are such that relatively little is known regarding the use of photochemical internalization to generate an immune response.

In particular, the breadth of the claims, in light of the limited disclosure of the specification, would not allow one of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

First note that it is clear that the photochemical method (employing certain disclosed agents) of the instant application (and the prior art) can be used to internalize exogenous molecules. The method of the instant claims, however, requires more. The claimed method requires the surface presentation of a sufficient amount of the internalized molecule to generate an immune response. Indeed, Claim 11 actually recites the stimulation of said response.

It is well-known in the immunological arts that only certain antigen presenting cells are capable of presenting antigens and generating an immune response. See, for example, Janeway et al. (1994) wherein it is taught that in addition to antigen presentation, costimulation that can only be provided by B cells,

macrophages, or dendritic cells, is required for the generation of an immune response. Accordingly, it appears that the method of Claims 2-5 and 7-11, employing any cell capable of photochemical internalization, could not be performed without an undue amount of experimentation.

Further regarding the breadth of the claims, the specification discloses only the actual use of $AlPcS_{2a}$ and $TPPS_{2a}$ as photochemical internalization agents. Claims 2-7 and 9-11 comprise either no limitations regarding photochemical internalization agents, or as in the case of Claim 7, are drawn to whole classes of agents including "derivatives thereof". The disclosure of two related species of agents cannot be considered to be reasonably sufficient to enable the method of the instant claims to be performed with any of the essentially unlimited number of disclosed families of chemicals (and derivatives thereof) without an undue amount of experimentation.

Finally, it remains the Examiner's position that the disclosure of the specification does not sufficiently demonstrate the required limitation that the claimed method be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response. As set forth previously, the specification fails to disclose any actual Class I MHC presentation. Indeed, the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangles of Figure 4 show a *lack* of antigen on the surface of the cells.

Applicant's arguments, filed 3/26/04 have been fully considered but they are not persuasive. Applicant begins by describing the experiments disclosed in the specification.

As set forth previously, for the reasons set forth previously, only Example 2 is relevant to the claimed invention, and it fails to disclose adequate controls. Examples 1 and 4 show only photochemical internalization. Example 3 demonstrates a *lack* of cell surface antigen presentation.

In regards to Example 2, applicant's assertion that, "Example 2 illustrates that MART-I peptides are expressed on the cell surface after use of the methods of the invention" is simply not factually correct. However, as set forth previously, in view of the 1.132. declaration of Inventor Hogset, filed 11/21/02, the Examiner has stipulated that the method of the example is enabled.

Applicant continues with additional discussions of the experiments set forth in the 1.132. declaration of Inventor Hogset.

A further review of the declaration shows no additional evidence for the enablement of the method of the instant claims. The additional experiments show only internalization of various molecules - no evidence of surface presentation, much less the generation of an immune response, is disclosed.

Applicant argues that photochemical internalization is possible with various cell types, antigens, and photosensitizers.

Regarding the various cell types and antigens, the Examiner agrees. However, regarding the different photosensitizers, the use of a few closely related agents is not representative, nor enabling of, the broad classes of agents set forth in the specification and claims. And again, the method of the claims requires much more than simple photochemical internalization.

Applicant continues, "The Examiner has further cited to a statement in a Declaration by Hogset (submitted November 18, 2002) that describes upon which factors cell death is principally dependent."

"Applicant submits that, contrary to the Examiner's allegations, the invention is not directed to killing cells. Instead the invention is directed to methods of expressing an antigenic molecule on the surface of a viable cell; In Example 2, cell death is caused by cytotoxic T cells, which are used simply as a way of confirming the existence of viable MART-I presenting cells prepared by the present methods. Discussion of cell death in the Hogset Declaration was directed to avoiding substantial cell death so that a viable cell could be generated that expressed the antigenic molecule of interest on its surface."

"Applicants submit that the confusion about cell killing may arise from confusion of the present methods with photodynamic therapeutic methods".

The Examiner was not confused by the declaration, it is the Examiner's position that the declaration indicated that certain factors, such as "the amount of toxic substances generated by the photosensitizing compounds on exposure to light and the presence and toxicity of molecules which are internalized during this process", factors not considered in the specification, are critical to the enablement of the method of the instant claims.

Applicant argues that in light of the teachings of WO96/07432 the method of the instant claims would require only routine optimization.

A review of WO96/07432 shows that the document reveals only the use of the same related photosensitizing agents as the instant application, and only for the internalization of toxins into tumor cells. There is no showing, nor even discussion, of cell surface presentation of said toxins nor the generation of an immune response. Accordingly, the document cannot be considered enabling for the invention of the instant claims.

6. The following are new grounds for rejection,

7. Claims 2-5 and 7-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, "a method of expressing an antigenic molecule on the surface of a viable cell...wherein, said released antigenic molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I MHC molecule.".

Upon careful review of the specification no support has been found for the broadening of the claimed invention, i.e., the specification discloses only a method comprising the required cell surface expression by a class I MHC molecule on an antigen presenting cell.

8. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of "a lysomotropic weak base or derivative" of "a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, or tetracycline".

The specification fails to disclose any species of the claimed reagents. Further, no definition is provided that would limit "lysomotropic weak bases or derivatives thereof". Accordingly, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

11. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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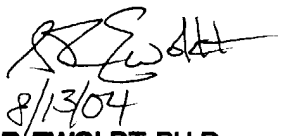

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PRIMARY EXAMINER